BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

STIC-ILL

From: STIC-Biotech/ChemLib
Sent: Tuesday, December 02, 2003 2:01 PM
To: STIC-ILL
Subject: FW: article request

-----Original Message-----
From: Lucas, Zacharia
Sent: Tuesday, December 02, 2003 1:57 PM
To: STIC-Biotech/ChemLib
Subject: article request

Examiner# : 79253 Zachariah Lucas
Art Unit : 1648
Phone Number: 308-4240
Date: 12-2-2003
Serial Number: 09/868177
MailBox & Bldg/Room Location: 8e12/8d16
Results Format Preferred (circle): Paper

Could you please send me a copy of the following article(s).

Tristram et al., Pediatr Ann. 1993 Dec;22(12):715-8.

Whimbey et al., Am J Med. 1997 Mar 17;102(3A):10-8; discussion 25-6.

Thank you,
Zac Lucas

National Library of Medicine

Entrez PubMed Nucleotide Protein Genome Structure PMC Journals

Search PubMed for RSV AND influenza AND combination Preview Go

Limits Preview/Index History Clipboard Details

- Search History will be lost after eight hours of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.

Entrez PubMed

PubMed Services

Related Resources

Search	Most Recent Queries	Time	Result
#15	Search **RSV AND influenza AND combination** Field: **Title/Abstract,** Limits: **Publication Date to 1999/12/16**	13:54:00	6
#14	Search **RSV AND influenza** Field: **Title/Abstract,** Limits: **Publication Date to 1999/12/16**	13:53:34	182
#8	Search **RSV AND influenza AND vaccine** Field: **Title/Abstract,** Limits: **Publication Date to 1999/12/16**	13:53:27	12
#7	Search **RSV AND influenza AND bivalent** Field: **Title/Abstract,** Limits: **Publication Date to 1999/12/16**	13:48:34	0
#6	Search **RSV AND influenza AND multivalent** Field: **Title/Abstract,** Limits: **Publication Date to 1999/12/16**	13:48:26	0
#2	Search **RSV AND subunit AND vaccine** Field: **Title/Abstract,** Limits: **Publication Date to 1999/12/16**	13:33:39	32
#1	Search **RSV AND subunit AND vaccine**	13:31:55	82

Clear History

Community Respiratory Virus Infections in Immunocompromised Patients with Cancer

Estella Whimbey, MD, Janet A. Englund, MD, Robert B. Couch, MD, *Houston, Texas*

Community respiratory viruses, such as respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, adenoviruses, and picornaviruses, are an important cause of respiratory disease in the immunocompromised adult with cancer. Recent studies have demonstrated that a minimum of 31% of adult bone marrow transplant (BMT) recipients and 18% of adults with leukemia who are hospitalized with an acute respiratory illness have a community respiratory virus infection. The temporal occurrence of these infections in immunocompromised patients tends to mirror their occurrence in the community. The clinical illnesses range from self-limited upper respiratory illnesses to fatal pneumonias, depending on the type of virus and the type and degree of immunosuppression. The pneumonias may be viral, bacterial/fungal, or mixed. The highest frequency of progression to fatal viral pneumonia has been reported for RSV infections in recently transplanted BMT recipients and myelosuppressed patients with leukemia. Studies have suggested that early therapy for RSV pneumonia with a combination of aerosolized ribavirin and intravenous immunoglobulin may be of benefit. Defining effective prophylactic and therapeutic strategies will be a challenge, given the diversity of viruses, the wide spectrum of immunocompromised patients with varying vulnerability to serious community respiratory virus disease, and the frequent presence of other opportunistic infections and medical problems. A combination of antiviral drugs and immunotherapy may need to be considered for their potential additive effect as well as to prevent the emergence of resistant virus, as occurs during monotherapy for influenza with amantadine or rimantadine. The optimal therapies need to be defined in controlled trials; however, it appears that a favorable response will hinge on the initiation of therapy at an early stage of the respiratory illness. ***Am J Med.*** **1997;102(3A):10–18.**

Over the past decade, there has been growing recognition that community respiratory viruses, such as respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, adenoviruses, and picornaviruses, are a frequent cause of serious respiratory disease among immunocompromised patients with cancer.[1-35] The emergence of these viruses in the setting of a growing population of severely immunodeficient patients has been coupled with an emergence of our knowledge of the frequency and the seriousness of community respiratory virus infections in immunocompromised patients in general.

Prior to 1991, community respiratory virus infections were uncommonly diagnosed at M. D. Anderson Cancer Center (MDACC). Similar to other cancer centers, respiratory viral disease was attributed primarily to the herpesviruses (particularly cytomegalovirus [CMV]) and occasional adenoviruses.[36] At that time, an intensive surveillance program was initiated in collaboration with the Acute Viral Respiratory Disease Unit of Baylor College of Medicine. It soon became apparent that community respiratory viruses were a frequent cause of acute upper as well as lower respiratory tract disease among immunocompromised adults with cancer.

During two consecutive winter seasons (November 1, 1992 to May 1, 1993 and November 1, 1993 to May 1, 1994), community respiratory virus infections were diagnosed in 67 (31%) of 217 adult bone marrow transplant (BMT) recipients hospitalized at MDACC with an acute respiratory illness.[34] This is a minimum estimate of the frequency of these infections, since all cases were confirmed by culture rather than by antigen detection, and serology was not performed. These infections were due to RSV (49%), influenza viruses (18%), picornaviruses (18%), parainfluenza viruses (9%), and adenoviruses (6%). The different viruses were intermingled through these two wintertime periods, as in the community. During the intervening warmer months, RSV and in-

From the Section of Infectious Diseases, The University of Texas M. D. Anderson Cancer Center and Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas.

Research performed by the authors was supported in part by Public Health Service Contract N01-AI-15103 from the National Institute of Allergy and Infectious Diseases.

Requests for reprints should be addressed to Estella Whimbey, MD, Section of Infectious Diseases (Box 47), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030.

0002-9343/97/$17.00
PII S0002-9343(97)00004-1

fluenza disappeared from our hospital as from the community.

The patients with community respiratory virus infections were young to middle-aged adults, an age group in which these viruses would typically cause relatively benign, self-limited illnesses. These infections were acquired by autologous (n = 32) as well as allogeneic (n = 35) transplant recipients, and by pre-engrafted (n = 28) as well as post-engrafted (n = 39) patients. However, the severity of some of the infections, particularly RSV, was temporally related to the time after transplant, with more severe infections tending to occur more frequently during the early post-transplant period. During these early years of the surveillance study, 32 (48%) infections were acquired nosocomially. The number of nosocomial infections has since declined considerably through an aggressive multifaceted infection-control strategy.[37] Only one infection was acquired in the protected environment, confirming that these infections did not primarily reflect reactivation of latent virus, as in the case of the herpesviruses, but were acquired exogenously.

In 28 (42%) patients, the illness remained limited to the upper respiratory tract and was characterized by rhinorrhea, nasal and sinus congestion, sore throat, and/or cough. None of these patients died. In 39 (58%) patients, the illness was complicated by pneumonia, which was either primary viral or secondary bacterial/fungal pneumonia. The overall mortality rate associated with pneumonia was high among autologous (12/20, 60%) as well as allogeneic BMT recipients (8/19, 42%). In contrast to pneumonias attributed to CMV, *Pneumocystis carinii*, or fungi, 85% of these pneumonias were preceded by an upper respiratory illness.

Autopsies were performed on 12 (60%) of the 20 patients who died. All 7 patients with RSV were documented to have extensive RSV pneumonia by histopathology and immunohistochemistry, one of whom also had candida pneumonia. Two of three patients with influenza had histopathology consistent with viral pneumonia and no other pathogens identified, as did both patients with picornavirus. Thus, autopsy examination confirmed the pulmonary invasiveness of the community respiratory viruses in adult BMT recipients.

In an era of reasonably effective prophylaxis for CMV disease, the community respiratory viruses have assumed a dominant role in the etiology of viral pneumonia in adult BMT recipients (**Table I**). During these two 6-month wintertime periods, pneumonias associated with community respiratory viruses occurred more than four times more frequently than those associated with CMV (18% vs 4%, respectively). The overall mortality attributable to pneumonias associated with community respiratory viruses was more than four times as high as that attributable to pneumonias associated with CMV (9% vs 2%, respectively).

TABLE I

Pneumonias Associated with Community Respiratory Viruses and Cytomegalovirus in 217 Adult Bone Marrow Transplant Recipients Hospitalized* with an Acute Respiratory Illness

	Community Respiratory Viruses	Cytomegalovirus
Pneumonia	39 (18%)	9 (4%)
Deaths	20 (9%)†	5 (2%)‡

*Nov 1 to May 1: 1992–93, 1993–94.
†12/20 autologous and 8/19 allogeneic bone marrow transplant (BMT) recipients died.
‡0/3 autologous and 5/6 allogeneic BMT recipients died.

Community respiratory viruses are also a frequent cause of acute upper and lower respiratory tract disease among hospitalized adults with leukemia.[30] During an 18-month period from November 1, 1993, to May 1, 1995, community respiratory virus infections were documented by culture in 60 (18%) of 335 adults with leukemia hospitalized at MDACC with an acute respiratory illness. The underlying diseases were acute myelogenous leukemia (n = 31), acute lymphocytic leukemia (n = 11), chronic myelogenous leukemia (n = 7), chronic lymphocytic leukemia (n = 4), and other leukemias (n = 7). The infections were due to influenza viruses (32%), RSV (30%), picornaviruses (17%), parainfluenza viruses (10%), adenoviruses (3%), and multiple community respiratory viruses (8%). A total of 13 (22%) infections were acquired nosocomially. Similar to the transplant patients, the temporal occurrence of these infections reflected their occurrence in the community. Infections due to RSV and influenza occurred during the cooler months of the year, whereas infections due to parainfluenza viruses, adenoviruses, and picornaviruses occurred year round.

In 22 (36%) patients, the illness remained confined to the upper respiratory tract and was characterized by rhinorrhea, nasal and sinus congestion, sore throat, and/or cough. None of these patients died. Similar to the transplant population, 38 (63%) infections were complicated by pneumonia, with an associated mortality of 47%. These pneumonias could be distinguished because the majority (84%) were preceded by an upper respiratory illness.

Autopsies were performed on 8 (44%) of the 18 patients with leukemia who died. In 6 cases the histopathology revealed viral inclusions and/or syncytial cells, confirming the diagnosis of viral pneumonia. The seventh patient had influenza A cultured from lung tissue and the eighth patient had diffuse,

nonspecific fibrotic pneumonitis. Three patients had concurrent fungal pneumonias.

The significant morbidity and mortality associated with community respiratory virus infections in patients with leukemia makes it clear that this is not a problem unique to patients with a most extreme global immunodeficiency, such as allogeneic BMT recipients. Community respiratory viruses are associated with serious pneumonias in a broader group of patients. Other patient populations at risk need to be identified.

RESPIRATORY SYNCYTIAL VIRUS

Of all the community respiratory viruses, RSV has received the most attention because it has been associated with an exceptionally high frequency of fatal viral pneumonia in certain subsets of patients.

TABLE II

Mortality Associated with Respiratory Syncytial Virus Pneumonia in Adult Bone Marrow Transplant Recipients and Adults with Leukemia

	Mortality (%)	
Therapy*	BMT (n = 23)	Leukemia (n = 17)
Early†	4/13 (31)	0/8 (0)
Early (noncompliant)	—	2/2 (100)
Early (6 h/day)	1/1 (100)	—
Late†	5/5 (100)	4/4 (100)
None	4/4 (100)	2/3 (66)

BMT = bone marrow transplant.
*Therapy consisted of aerosolized ribavirin (20 mg/mL for 18 h/day) and intravenous immunoglobulin (IV Ig; 500 mg/kg every other day). One patient received aerosolized ribavirin (60 mg/mL for 2 h every 8 h) and IV Ig.
†Therapy was classified as "early" or "late" depending on whether it was initiated >24 h or <24 h prior to respiratory failure requiring mechanical ventilation, respectively.

BMT Recipients

Among immunocompromised adults, only sporadic cases of RSV disease had been reported until 1988, when Englund et al[5] described serious RSV disease in 11 immunocompromised adults. This study, together with subsequent studies of BMT recipients at the University of Minnesota, the Fred Hutchinson Cancer Research Center (FHCRC), and other centers, established several salient features of the disease.[6,8,11,12,17] RSV was not only capable of causing serious pneumonias in adult BMT recipients, but it did so frequently during community outbreaks. RSV infections in adult BMT recipients followed the same clinical sequence as in children, with upper respiratory illness preceding pneumonia. The frequency of progression to pneumonia was highest in pre-engrafted transplant recipients; however, the mortality associated with pneumonia was similarly high in pre- and post-engrafted patients. Aerosolized ribavirin alone appeared to be of some benefit if it was started prior to the onset of pneumonia; if it was started after the onset of pneumonia, the mortality rate was >70%.

In 1992, a therapeutic trial of combination antiviral therapy and immunotherapy for RSV pneumonia was initiated at MDACC. Previous studies had suggested that aerosolized ribavirin alone was not effective, and there were promising reports of the potential beneficial effects of immunoprophylaxis as well as immunotherapy for RSV infections in vitro, in animal studies, and in children.[27,28,31,34,38-44] Therapy consisted of aerosolized ribavirin (20 mg/mL for 18 h/day) and intravenous immunoglobulin (IV Ig; 500 mg/kg every other day). In the first 2 years of the study, selected lots of IV Ig were chosen that contained substantial RSV microneutralization antibody titers (1:2048 to 1:8102 to RSV subtype A).[44]

Between November 1992 and November 1995, RSV infections were diagnosed by culture or autopsy in 38 hospitalized adult BMT recipients.[27,34] The cases occurred during 9- to 16-week wintertime periods and accounted for a significant proportion of the respiratory illnesses occurring among hospitalized adult BMT recipients (19/41 [45%], 12/55 [22%], and 7/52 [14%], respectively). The declining frequency of infections in the second and third year was attributable primarily to a more aggressive infection-control strategy[27] and to a new policy of postponing transplantation in patients with upper respiratory illnesses.

All 38 patients presented with an upper respiratory illness. Pneumonia developed in 23 (61%) patients (Table II). The mortality rate was 31% among patients with pneumonia in whom combination therapy was initiated >24 hours prior to respiratory failure requiring mechanical ventilation (n = 13). In contrast, the mortality rate was 100% among patients who were treated after the onset of respiratory failure (n = 5), patients who were not treated (n = 4), and the one patient treated with high-dose short-duration aerosolized ribavirin.[45,46]

Some centers have tried other treatment regimens with varying success, including combination aerosolized and intravenous ribavirin.[47] The relative ease of administration of intravenous ribavirin is attractive. However, in a recent trial, the mortality rate was 80% among 10 BMT recipients with RSV pneumonia treated with intravenous ribavirin.[32] The dose of ribavirin used in this study was considerably lower than that used to treat hemorrhagic fevers, raising the question of whether a higher dose might be of benefit at an earlier stage of the respiratory illness.[48,49] Since the response to therapy will vary considerably depending on the stage of the respiratory

TABLE III

Frequency and Outcome of Pneumonia Related to Post-Transplant Time in 46* Adult Bone Marrow Transplant Recipients with Respiratory Syncytial Virus Infections

	Time After Transplant		
	≤1 Month (n = 23)	>1 to ≤2 Months (n = 6)	>2 Months (n = 17)
URI	7 (30%)†	3 (50%)†	13 (76%)†
Pneumonia	16 (70%)	3 (50%)	4 (24%)
Deaths	10 (63%)	2 (66%)	2 (50%)

URI = upper respiratory illness.
*All 46 patients presented with a URI; 23 patients subsequently developed pneumonia.
†5/7, 2/3, and 3/13 patients with URIs were treated pre-emptively with aerosolized ribavirin and intravenous immunoglobulin, with resolution of the illness.

TABLE IV

Outcome of Respiratory Syncytial Virus and Cytomegalovirus Pneumonia in Adult Bone Marrow Transplant Recipients

	Mortality (%)	
Therapy*	RSV (n = 23)†	CMV (n = 29)‡
Early§	4/13 (31)	7/12 (58)
Early (6 h/day)	1/1 (100)	—
Late§	5/5 (100)	11/11 (100)
None	4/4 (100)	5/6 (83)
Overall	14/23 (61)	23/29 (79)

RSV = respiratory syncytial virus; CMV = cytomegalovirus.
*Therapy for CMV pneumonia consisted of ganciclovir (or occasionally foscarnet) and intravenous immunoglobulin (IV Ig, 500 mg/kg every other day). Therapy for RSV pneumonia consisted of aerosolized ribavirin (20 mg/mL for 18 h/day) and IV Ig (500 mg/kg every other day). One patient received aerosolized ribavirin (60 mg/mL for 2 h every 8 h) and IV Ig.
†23 consecutive cases of RSV pneumonia occurring in adult bone marrow transplant (BMT) recipients hospitalized at M. D. Anderson Cancer Center (MDACC) from November 1992 to November 1995.
‡29 consecutive cases of CMV pneumonia occurring in allogeneic BMT recipients hospitalized at MDACC during 1991–1994.
§Therapy was classified as "early" or "late" depending on whether it was initiated >24 h or <24 h prior to respiratory failure requiring mechanical ventilation, respectively.

TABLE V

Outcome Associated with Pre-emptive Therapy* for Upper Respiratory Illness in 12 Adult Bone Marrow Transplant Recipients with Respiratory Syncytial Virus Infections

	Time After Transplant		
	≤1 Month (n = 7)	>1 to ≤2 Months (n = 2)	>2 Months (n = 3)
Resolution of illness	5	2	3
Progression to pneumonia	2	0	0

*Therapy consisted of aerosolized ribavirin and intravenous immunoglobulin (500 mg/kg every other day). Aerosolized ribavirin was administered at a dose of 20 mg/mL for 18 h/day to 5 patients (one of whom developed pneumonia and died) and a dose of 60 mg/mL for 2 h every 8 h to 7 patients (one of whom developed pneumonia and died).

illness as well as the type, degree, and duration of underlying immunodeficiency, the optimal therapy will need to be defined in controlled trials.

The risk of pneumonia and death was closely related to the time after transplant (**Table III**). During these 3 years, RSV infection was documented by viral culture or autopsy in 46 adult BMT recipients (38 inpatients and 8 outpatients). Sixteen (70%) of the 23 patients who were ≤1 month post-transplant developed pneumonia. This is a minimum estimate, since 5 of the 7 patients with upper respiratory illnesses who were ≤1 month post-transplant were treated pre-emptively with combination aerosolized ribavirin and IV Ig. These patients may have developed pneumonia had they not been treated. In contrast, only 4 (24%) of the 17 patients who were >2 months post-transplant developed pneumonia, 2 of whom died. These 2 patients had a relapse of leukemia and profound chemotherapy-induced myelosuppression.

There are several striking similarities between the outcome and response to therapy for RSV pneumonia with aerosolized ribavirin and IV Ig and the outcome and response to therapy for CMV pneumonia with ganciclovir and IV Ig (**Table IV**). In spite of an intensive surveillance system for both RSV and CMV disease, ≥39% of these viral pneumonias have been diagnosed only after the onset of respiratory failure or death, resulting in a mortality rate approaching 100%. Even when therapy has been initiated before the onset of respiratory failure, the mortality rates associated with RSV and CMV pneumonia have been high (31% and 58%, respectively). Because of the high overall mortality rate with viral pneumonia (61% for RSV pneumonia and 79% for CMV pneumonia), the approach to RSV disease will probably need to be modeled after the strategies that have been worked out for CMV disease, namely, prophylaxis or pre-emptive therapy at an early stage of the viral illness. For RSV disease, pre-emptive therapy will require treating high-risk patients who have upper respiratory illnesses.

During the three wintertime periods studied at MDACC, pre-emptive therapy with a combination of aerosolized ribavirin and IV Ig (500 mg/kg every other day) was administered to 12 BMT recipients with upper respiratory illnesses (**Table V**). Aerosolized ribavirin was administered at a dose of 20 mg/mL for 18 h/day to 5 patients and at a dose of 60 mg/mL for 2 hours every 8 hours to 7 patients.[45,46] In 10 of the 12 patients, the illnesses remained confined to the upper respiratory tract and the patients survived; the other 2 patients (both autologous BMT recipients) died of RSV pneumonia. One of the patients who died had prolonged marrow aplasia due to graft failure and developed progressive RSV pneumonia while receiving the 6 h/day regimen. The other pa-

tient who died had complete resolution of the respiratory illness on the 18 h/day regimen and was discharged home, but returned 1 month later with fulminant RSV pneumonia and subsequently died. It is not clear if this represented relapse of infection or reinfection. Controlled clinical trials are needed to evaluate the optimal pre-emptive therapy.

Patients with Leukemia

The epidemiology, clinical course, and response to therapy for RSV infection in adults with leukemia mirrored the findings in adult BMT recipients. Between November 1993 and November 1996, RSV was documented by culture in 31 adults with leukemia cared for at MDACC.[31] All cases occurred during the winter months, when RSV was prevalent in the community. As in the transplant recipients, the onset of illness was characterized by an upper respiratory illness in all patients. The frequency of progression to pneumonia was considerably higher among myelosuppressed (absolute neutrophil count ≤500/mL) than among non-myelosuppressed patients, as it had been higher among more recently transplanted, more myelosuppressed BMT recipients. Thus, the upper respiratory illnesses were complicated by pneumonia in 15 (71%) of 21 patients who were myelosuppressed compared with 2 (20%) of 10 patients who were not myelosuppressed. The mortality rate associated with pneumonia in the setting of myelosuppression was high (53%). In contrast, none of the 10 non-myelosuppressed patients died.

Prompt therapy for RSV pneumonia with aerosolized ribavirin (20 mg/mL for 18 h/day) and IV-Ig at an early stage of the pneumonia was associated with a favorable outcome (Table II). None of the 8 patients in whom therapy was initiated >24 hours prior to intubation died (6 patients were myelosuppressed). In contrast, the mortality rate was 89% among patients who received no therapy (n = 3), patients who began therapy after the onset of respiratory failure (n = 4), and patients who were unable to tolerate the therapy (n = 2).

Autopsies were performed on 10 adults with leukemia and BMT recipients who died with RSV pneumonia. In all 10 cases, histopathology and immunohistochemical studies confirmed the diagnosis of invasive RSV pneumonia. Three patients also had other pulmonary pathogens.

In summary, RSV is a frequent cause of life-threatening pneumonia in some subsets of adults with leukemia and BMT recipients. Other high-risk patients need to be identified. The optimal therapy and route of administration need to be defined in controlled trials. It appears that a favorable response will hinge on the initiation of therapy at an early stage of the pneumonia. In some subsets of patients with a high frequency of progression to pneumonia, pre-emptive therapy for upper respiratory illnesses will need to be considered. The simplest and most effective therapy is prevention, through infection-control measures and postponement or dose-modification of chemotherapy (if feasible), in high-risk patients with RSV upper respiratory illnesses. Whether prophylactic high-titered RSV immunoglobulin will be of benefit in these patients, as it has been in young children, needs to be studied.[43]

INFLUENZA VIRUS

Influenza is considered to be one of the most important respiratory diseases of mankind. The Centers for Disease Control have long recommended that immunocompromised patients receive annual influenza vaccination or chemoprophylaxis with amantadine/rimantadine during the influenza season.[50] This has been an uncommon practice in cancer centers, in part because of the skepticism that severely immunocompromised patients will be able to mount a protective antibody response to active immunization[51–54] and in part because of the paucity of data documenting the morbidity and mortality of influenza in these patients.

Since 1991, we have actively looked for influenza as part of our general surveillance for community respiratory viruses. Similar to RSV, the occurrence of influenza in hospitalized immunocompromised adults has mirrored the occurrence of influenza in the community. During three wintertime periods lasting from 6 to 12 weeks each, influenza was documented by culture in approximately 10–30% of adults with leukemia and BMT recipients hospitalized at MDACC with an acute respiratory illness.

Closer evaluation of 27 adults with leukemia and 20 adult BMT recipients with culture-confirmed influenza hospitalized at MDACC during three winter outbreaks revealed that these illnesses were associated with significant morbidity and mortality.[21,30,31,55] The clinical course of influenza was similar in the two subsets of patients (Table VI). Overall, the illness was complicated by pneumonia in 75% of the patients and the pneumonia-associated mortality rate was 40%. Although this mortality rate is not as dramatically high as that of RSV pneumonia, it is nonetheless high. The high frequency of pulmonary complications and death highlights the need for aggressive prophylactic strategies.

Autopsy examination of 10 patients who died with influenza revealed a histopathology consistent with viral pneumonia in 8 patients, 3 of whom also had other pulmonary pathogens. The other 2 patients on whom autopsies were performed had bacterial and/or fungal pneumonia.

TABLE VI

Frequency of Pneumonia and Outcome of Influenza Among Hospitalized Adult Bone Marrow Transplant Recipients and Adults with Leukemia

	BMT (n = 20)*	Leukemia (n = 27)†
Pneumonia	14 (70%)	21 (78%)
Deaths	5 (36%)	9 (43%)

BMT = bone marrow transplant.
*These 20 cases occurred during the winters of 1991–92, 1992–93, and 1993–94: 17 cases were type A influenza; 3 were type B influenza.
†These 27 cases occurred during the winters of 1991–92, 1993–94, and 1994–95: All were type A influenza.

TABLE VII

Outcome of Parainfluenza Virus-Associated Pneumonia Among Hospitalized Adult Bone Marrow Transplant Recipients and Patients with Leukemia

	Mortality (%)	
Therapy*	BMT (n = 26)	Leukemia (n = 6)
Early†	0/3 (0)	—
Late†	2/2 (100)	—
None	8/21 (38)	4/6 (66)

BMT = bone marrow transplant.
*Therapy consisted of aerosolized ribavirin (20 mg/mL for 18 h/day) and intravenous immunoglobulin (500 mg/kg every other day for varying durations).
†Therapy was classified as "early" or "late" depending on whether it was initiated >24 h or <24 h prior to respiratory failure requiring mechanical ventilation, respectively.

Although influenza has been studied globally for decades there are no guidelines for the treatment of influenza pneumonia and it is not known whether amantadine/rimantadine can prevent the progression of uncomplicated influenza to pneumonia in an immunocompromised patient. Studies have suggested that amantadine/rimantadine and/or ribavirin (aerosolized or intravenous) may be of benefit.[66–70]

In our study, many patients were treated with amantadine/rimantadine and a few patients also received ribavirin. However, this was not done in a systematic manner (in part because of an inability to diagnose these illnesses in a timely manner), and the efficacy of therapy could not be evaluated. Nevertheless, several important findings emerged. Similar to viral pneumonias caused by RSV and CMV, antiviral therapy was not of benefit if it was initiated after the onset of respiratory failure. Also, similar to immunocompetent patients, a significant proportion of immunocompromised patients treated with amantadine/rimantadine alone developed resistant strains of virus, suggesting that amantadine/rimantadine alone may not be an option for the therapy of influenza A in these patients.[71–74] Effective therapeutic regimens for influenza virus pneumonia need to be established for immunocompetent as well as immunocompromised patients. A combination of antiviral drugs (such as rimantadine, ribavirin, and/or neuraminidase inhibitors) needs to be investigated, as well as the potential additive benefit of immunotherapy.[75,76]

There have been other reports of influenza in immunocompromised adults that have not documented such a high frequency of pulmonary complications and death.[2,7,18] This wide spectrum of observations probably reflects the wide spectrum of immunocompromised patients being studied. The morbidity and mortality of influenza, as well as the other community respiratory viruses, appear to be related to the type, degree, and duration of immunosuppression. In less immunocompromised patients, the clinical course of influenza may be more comparable to that in immunocompetent persons. It is also noteworthy that, unlike RSV, influenza viruses undergo frequent antigenic variation and prevalent types and serotypes vary, so the morbidity and mortality may be expected to vary from year to year.

PARAINFLUENZA VIRUSES

Parainfluenza viruses rarely cause more than a self-limited upper respiratory illness in adults. The importance of parainfluenza viruses as a cause of life-threatening pneumonia in severely immunocompromised adults was highlighted in two studies from the University of Minnesota and MDACC in the early 1990s, describing 12 and 8 adult BMT recipients, respectively.[15,19]

The epidemiology, frequency, and clinical course of 61 adult BMT recipients with culture-confirmed parainfluenza virus infection who were cared for at MDACC over a 3-year period from January 1991 to September 1994 were recently reviewed.[33] The overall frequency of infection was 5%, which was similar to the 2% frequency noted in the University of Minnesota study. Although these infections occurred throughout the year, most cases occurred in the spring or summer. More than half (53%) of the cases occurred in the spring and summer of 1994, highlighting the need to anticipate outbreaks of infections. During this outbreak period, parainfluenza viruses were isolated from one third (32/96) of the adult BMT recipients hospitalized with an acute respiratory illness.

The clinical course and outcome of parainfluenza virus infection among hospitalized patients with leukemia have mirrored the experience with hospitalized BMT recipients.[30,31] Among 45 consecutive BMT recipients and 9 consecutive patients with leukemia (all myelosuppressed) who were hospitalized with parainfluenza virus infections, the illness was complicated by pneumonia in 26 (58%) and 6 (66%) cases,

respectively. More than 80% of the pneumonias were preceded by an upper respiratory illness. The overall mortality rate with pneumonia was high: 39% and 66%, respectively.

Autopsy examination of 7 patients revealed a histopathology consistent with viral pneumonia in 6 patients and diffuse fibrotic pneumonitis in the seventh patient. Four patients had serious concurrent opportunistic infections, a finding that highlights the profound immunodeficiency of these patients.

There is no established therapy for parainfluenza virus infections. In vitro data and anecdotal reports have suggested that ribavirin may be of benefit. In the University of Minnesota study, 9 patients were treated with aerosolized ribavirin without apparent benefit. In this study, 3 BMT recipients with pneumonia were treated promptly with a combination of aerosolized ribavirin and IV Ig and survived (**Table VII**). However, 15 (47%) patients survived without antiviral therapy, suggesting that many pneumonias were self-limited viral pneumonias and/or bacterial/fungal superinfections. The significant number of pneumonias that resolved with antibacterial/antifungal therapy alone as well as the high frequency of concurrent opportunistic infections (which may mask a potential benefit of therapy) make it clear that therapeutic trials for parainfluenza virus-associated pneumonia will need to be controlled. Therapeutic trials will also require the routine availability of a rapid diagnostic test for parainfluenza virus, as is currently available for RSV, since culture results frequently become available only after the onset of respiratory failure.

ADENOVIRUSES

Adenoviruses have been the most extensively studied community respiratory virus in immunocompromised patients.[3,11,21] Adenoviruses are distinguished from the other community respiratory viruses because they are DNA, rather than RNA, viruses and are thought to be acquired endogenously by reactivation as well as exogenously. Adenoviruses typically cause a wide range of clinical syndromes, including respiratory tract disease, urinary tract disease, enterocolitis, hepatitis, encephalitis, and disseminated disease.

Between March 1991 and May 1995, adenoviruses were cultured from the respiratory tract of 28 adult BMT recipients cared for at MDACC.[24] Fifteen (54%) patients survived, including 10 patients with upper respiratory illnesses and 5 patients with pneumonia (one of whom was treated with intravenous ribavirin). Thirteen (46%) patients died, including 7 patients with pneumonia and 6 patients with disseminated disease. The majority of the pneumonias were not preceded by an upper respiratory illness. Seven patients who died were treated with intravenous ribavirin without apparent benefit; however, in all cases, therapy was initiated after the onset of disseminated disease or multi-organ failure. Risk factors for fatal disease included the isolation of adenovirus from multiple sites and prolonged shedding. Other risk factors need to be identified and rapid diagnostic tests need to be developed so that patients can be recognized early for potential therapies. The optimal therapy needs to be defined, including the role of immunoglobulins and adoptive immunotherapy with donor leukocytes.[77]

PICORNAVIRUSES AND CORONAVIRUSES

Our understanding of the role of picornaviruses (rhinoviruses and enteroviruses) in the immunocompromised patient is minimal. Since 1991, >130 picornavirus infections have been identified among our adults with leukemia and BMT recipients; >90% of the isolates tested thus far have been rhinoviruses. In the majority of these patients, the illnesses have been limited to the upper respiratory tract or have been complicated by pneumonias, which appear to have been bacterial or fungal in origin. However, some patients have had a clinical course consistent with viral pneumonia and have died of unexplained interstitial pneumonias. Analysis of this experience is under way.

Coronaviruses, which are one of the most frequent causes of acute respiratory illness in the community, are difficult to isolate in clinical specimens and have not been systematically looked for in immunocompromised patients.

CONCLUSION

Immunocompromised patients do not live on a protected island. They are part of the community and are susceptible to the same respiratory viral infections that so frequently afflict the other members of the community. In some subsets of immunocompromised patients, these commonplace, otherwise trivial illnesses may be associated with serious morbidity and mortality. For most of these viruses, there are only limited means of identifying infections in a timely, clinically useful manner and there are almost no guidelines for effective prevention and treatment. In addition, there are few therapeutic options to choose from and their efficacy has not been established.

Because of the large number of patients who are seriously ill with these diseases, effective prophylactic and therapeutic regimens need to be defined. This will be a challenge, since there is a wide diversity of viruses, each of which needs to be approached individually, and there is a wide range of immunocompromised patients with varying vulnerability to seri-

ous community respiratory virus disease. Even within a particular subset of patients, such as leukemia patients and BMT recipients, there is a wide range of vulnerability to serious disease that is often in a state of flux, reflecting their worsening or improving immunodeficiency. Further confounding the clinical picture is the frequent presence of other serious opportunistic infections and medical problems. To conduct the controlled trials needed to define effective prophylactic and therapeutic regimens, many of these complex problems will need to be addressed collaboratively by the multiple medical centers caring for these patients.

REFERENCES

1. Couch RB. Respiratory diseases. In: Galasso GJ, Whitley RJ, Merigan TC, eds. *Antiviral Agents and Viral Diseases of Man*. 3rd ed. New York: Raven Press Ltd; 1990:327–372.
2. Feldman S, Webster RG, Sugg M. Influenza in children and young adults with cancer. *Cancer*. 1977;39:350–353.
3. Shields AF, Hackman RC, Fife KH, et al. Adenovirus infections in patients undergoing bone-marrow transplantation. *N Engl J Med*. 1985;312:529–533.
4. Hall CB, Powell KR, MacDonald NE, et al. Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med*. 1986;315:77–81.
5. Englund JA, Sullivan CJ, Jordan C, et al. Respiratory syncytial virus infections in immunocompromised adults. *Ann Intern Med*. 1988;109:203–208.
6. Martin MA, Bock MJ, Pfaller MA, Wenzel RP. Respiratory syncytial virus infections in adult bone marrow transplant recipients. *Lancet*. 1988;1396–1397.
7. Aschan J, Ringden O, Ljungman P, et al. Influenza B in transplant patients. *Scand J Infect Dis*. 1989;21:349–350.
8. Hertz MI, Englund JA, Snover D, et al. Respiratory syncytial virus-induced acute lung injury in adult patients with bone marrow transplants: a clinical approach and review of the literature. *Medicine*. 1989;68:269–281.
9. Kempe A, Hall CB, MacDonald NE, et al. Influenza in children with cancer. *J Pediatr*. 1989;115:33–39.
10. Ljungman P, Gleaves CA, Meyers JD. Respiratory virus infections in immunocompromised patients. *Bone Marrow Transplant*. 1989;4:35–40.
11. Fouillard L, Mouthon L, Laporte JP, et al. Severe respiratory syncytial virus pneumonia after autologous bone marrow transplantation: a report of three cases and review. *Bone Marrow Transplant*. 1992;9:97–100.
12. Harrington RD, Hooton RD, Hackman RC, et al. An outbreak of respiratory syncytial virus in a bone marrow transplant center. *J Infect Dis*. 1992;165:987–993.
13. Hierholzer JC. Adenoviruses in the immunocompromised host. *Clin Microbiol Rev*. 1992;5:262–274.
14. Hirschhorn LR, McIntosh K, Anderson KG, Dermody TS. Influenza pneumonia as a complication of autologous bone marrow transplantation. *Clin Infect Dis*. 1992;14:786–787.
15. Wendt CH, Weisdorf DJ, Jordan MC, et al. Parainfluenza virus respiratory infection after bone marrow transplantation. *N Engl J Med*. 1992;326:921–926.
16. Whimbey E, Bodey GP. Viral pneumonia in the immunocompromised adult with neoplastic disease: the role of common community respiratory viruses. *Semin Respir Infect*. 1992;7:122–131.
17. Winn N, Mitchell D, Pugh S, Russell NH. Successful therapy with ribavirin of late onset respiratory syncytial virus pneumonitis complicating allogeneic bone marrow transplantation. *Clin Lab Haematol*. 1992;14:29–32.
18. Ljungman J, Andersson J, Aschan J, et al. Influenza A in immunocompromised patients. *Clin Infect Dis*. 1993;17:244–247
19. Whimbey E, Vartivarian SE, Champlin R, et al. Parainfluenza virus infection in adult bone marrow transplant patients. *Eur J Clin Microbiol Infect Dis*. 1993;12:699–701.
20. Bowden RA. Other viruses after marrow transplantation. In: Forman SJ, Blume KG, Thomas ED, eds. *Bone Marrow Transplantation*. Cambridge, MA: Blackwell Scientific Publications;1994:443–453.
21. Flomenberg P, Babbitt J, Drobyski WR, et al. Increasing incidence of adenovirus disease in bone marrow transplant recipients. *J Infect Dis*.1994;169:775–781.
22. Whimbey E, Elting LS, Couch RB, et al. Influenza A virus infection among hospitalized adult bone marrow transplant recipients. *Bone Marrow Transplant*. 1994;13:437–440.
23. Elting LS, Whimbey E, Lo W, et al. Epidemiology of influenza A virus infection in patients with acute or chronic leukemia. *Support Care Cancer*. 1995;3:198–202.
24. Mirza N, Whimbey E, Champlin R, et al. Adenovirus in adult bone marrow transplantation (BMT) recipients. (Abstr.) *Blood*. 1995;86:218A.
25. Sable CA, Haydn FG. Orthomyxoviral and paramyxoviral infections in transplant patients. *Infect Dis Clin N Am*. 1995;9:987–1003.
26. Wendt CH, Hertz MI. Respiratory syncytial virus and parainfluenza virus infections in the immunocompromised host. *Semin Respiratory Infections*. 1995;10:224–231.
27. Whimbey E, Champlin R, Englund JA, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. *Bone Marrow Transplant*. 1995;16:393–399.
28. Whimbey E, Couch R, Englund J, et al. Respiratory syncytial virus pneumonia among hospitalized adult patients with leukemia. *Clin Infect Dis*. 1995;21:376–379.
29. DeVincenzo JP, Leombuno D, Soiffer RJ, Siber GR. Immunotherapy of respiratory syncytial virus pneumonia following bone marrow transplantation. *Bone Marrow Transplant*. 1996;17:1051–1056.
30. Ladisla B, Englund J, Couch R, et al. Community respiratory virus infections in hospitalized adult patients with leukemia. Abstracts of the Infectious Diseases Society of America; New Orleans, Lousiana, 1996. Abstract No. 99.
31. Ladisla B, Englund J, Couch R, et al. Respiratory syncytial virus disease among hospitalized adult immunocompromised patients with leukemia. Abstracts of the Infectious Diseases Society of America; New Orleans, Lousiana, 1996. Abstract No. 100.
32. Lewinsohn DM, Bowden RA, Mattson D, Crawford SW. Phase I study of intravenous ribavirin treatment of respiratory syncytial virus pneumonia after marrow transplantation. *Antimicrobial Agents Chemother*.1996;40: 2555–2557.
33. Lewis V, Champlin R, Englund J, et al. Respiratory disease due to parainfluenza virus in adult bone marrow transplant recipients. *Clin Infect Dis*. 1996;23:1033–1037.
34. Whimbey E, Champlin R, Couch R, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. *Clin Infect Dis*. 1996;22:778–782.
35. Yousuf HM, Englund J, Couch R, et al. Influenza among hospitalized adults with leukemia. *Clin Infect Dis*. In press.
36. Meyers JD, Flournoy N, Thomas ED. Nonbacterial pneumonia after allogeneic marrow transplantation: a review of ten years' experience. *Rev Infect Dis*. 1982;4:1119–1132.
37. Raad I, Abbas A, Whimbey E. Infection control of nosocomial respiratory viral disease in the immunocompromised host. *Am J Med*. 1997;102(suppl)[THIS ISSUE].
38. Hall CB, McBride JT, Walsh EE, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial virus infection: a randomized double-blind study. *N Engl J Med*. 1983;308:1443–1447.
39. Hemming VS, Prince GA, Horswood RL, et al. Studies of passive immunotherapy for infections of respiratory syncytial virus in the respiratory tract of a primate model. *J Infect Dis*. 1985;152:1083–1087.
40. Prince GA, Hemming GV, Horswood RL, Chanock RM. Immunoprophylaxis and immunotherapy for respiratory syncytial virus infection in the cotton rat. *Virus Res*. 1985;3:193–206.
41. Gruber WC, Wilson SZ, Throop BJ, Wyde PR. Immunoglobulin administration and ribavirin therapy: efficacy in respiratory syncytial virus infection of the cotton rat. *Pediatr Res*.1987;21:270–275.

42. Hemming VG, Rodriguez W, Kim HW, et al. Intravenous immunoglobulin treatment of respiratory syncytial virus infections in infants and young children. *Antimicrobial Agents Chemother.* 1987;31:1882–1886.
43. Groothuis JR, Simoes EAF, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *N Engl J Med.* 1993;329:1524–1530.
44. Siber GR, Leombruno D, Leszczynski J, et al. Comparison of antibody concentrations and protective activity of respiratory syncytial virus immune globulin and conventional immune globulin. *J Infect Dis.* 1993;169:1368–1373.
45. Englund JA, Piedra PA, Ahn Y, et al. High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *J Pediatr.* 1994;125:636–641.
46. Whimbey E, Champlin R, Englund J, et al. High-dose, short-duration aerosolized ribavirin for respiratory syncytial virus disease in adult BMT recipients. Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy; Orlando, Florida; 1994. Abstract No. H88.
47. Ljungman P. Respiratory virus infections in bone marrow transplant recipients: the European perspective. *Am J Med.* 1997;102(suppl) [THIS ISSUE]
48. McCormick JB, King LJ, Webb PA, et al. Lassa fever: effective therapy with ribavirin. *N Engl J Med.* 1986;314:20–26.
49. Huggins JW, Hsiang CM, Cosgriff TM, et al. Prospective double-blind concurrent placebo-controlled clinical trial of intravenous ribavirin therapy for hemorrhagic fever with renal syndrome. *J Infect Dis.* 1991;164:1119–1127.
50. Centers for Disease Control. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 1995;45 (RR-5):1–26.
51. Orbtzis DW, Liethaber H, Presant CA, et al. Influenza immunization in adult patients with malignant disease. *Ann Intern Med.* 1977;87:552–557.
52. Gross PA, Gould AL, Brown AE. Effect of cancer chemotherapy on the immune response to influenza virus vaccine: review of published studies. *Rev Infect Dis* 1985;7:613–618.
53. Engelhard D, Ragar A, Hardan I, et al. Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell depleted and autologous BMT recipients. *Bone Marrow Transplant.* 1993;11:1–5.
54. Lo W, Whimbey E, Elting L, et al. Influenza vaccination in adult lymphoma patients during chemotherapy: antibody response to a two-dose vaccine regimen. *Eur J Clin Microbiol Infect Dis.* 1993;12:778–781.
55. Monto AS, Gunn RA, Bandyk MG, King CL. Prevention of Russian influenza by amantadine. *JAMA* 1979;241:1003–1007.
56. Wilson SZ, Knight V, Wyde PR, et al. Amantadine and ribavirin aerosol treatment of influenza A and B infection in mice. *Antimicrob Agents Chemother.* 1980;17:642–648.
57. Knight V, McClung HW, Wilson SZ, et al. Ribavirin small-particle aerosol treatment of influenza. *Lancet.* 1981;ii:945–949.
58. Dolin R, Reichman RC, Madore HP, et al. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med.* 1982;307:580–584.
59. McClung HW, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of influenza B virus infection. *JAMA.* 1983;249:2671–2674.
60. Wilson SZ, Gilbert BE, Quarles JM. Treatment of influenza A (H1N1) virus infection with ribavirin aerosol. *Antimicrob Agents Chemother.* 1984;26:200–203.
61. Gilbert BE, Wilson SZ, Knight V, et al. Ribavirin small-particle aerosol treatment of infections caused by influenza virus strains A/Victoria/7/83 (H1N1) and B/Texas/1/84. *Antimicrob Agents Chemother.* 1985;27:309–313.
62. Hall CB, Dolin R, Gala CL, et al. Children with influenza A infection: Treatment with rimantadine. *Pediatrics.* 1987;80:275–282.
63. Knight V, Gilbert BE. Ribavirin aerosol treatment of influenza. *Antiviral Chemother.* 1987;1:441–457.
64. Stein DS, Creticos CM, Jackson GG, et al. Oral ribavirin treatment of influenza A and B. *Antimicrobial Agents Chemother.* 1987;31:1285–1287.
65. Bell M, Hunter JM, Mostaf SM. Nebulised ribavirin for influenza B viral pneumonia in a ventilated immunocompromised adult. *Lancet* 1988;2:1084–1085.
66. Ray CG, Icenogle TB, Minnich LL, et al. The use of intravenous ribavirin to treat influenza virus-associated acute myocarditis. *J Infect Dis.* 1989;159:829–836.
67. Douglas RG Jr. Prophylaxis and treatment of influenza. *N Engl J Med.* 1990;332:443–450.
68. Gilbert BE, Knight V. Ribavirin aerosol as the treatment for influenza. *Drugs of Today.* 1990;26:195–205.
69. Rodriguez WJ, Hall CB, Welliver R, et al. Efficacy and safety of aerosolized ribavirin in young children hospitalized with influenza: a double-blind, multicenter, placebo-controlled trial. *J Pediatr.* 1994;125:129–135.
70. Hayden FG, Sabie CA, Connor JD, Lane J. Intravenous ribavirin by constant infusion for serious influenza and parainfluenza virus infection. *Antiviral Therapy.* 1996;1:51–56
71. Hayden FG, Belshe RB, Clover RD, et al. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med.* 1989;321:1696–1702.
72. Mast EEL, Harmon MW, Gravenstein S, et al. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of Influenza A (H3N2). *Am J Epidemiol.* 1991;134:988–997.
73. Klimov AI, Rocha E, Hayden FG, et al. Prolonged shedding of amantadine-resistant influenza A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. *J Infect Dis.* 1995;172:1352–1355.
74. Englund JA, Champlin RE, Yousuf H, et al. Disease due to rimantadine/amantadine-resistant influenza virus in bone marrow transplant recipients: a prospective study. ICAAC; New Orleans, Louisiana; September, 1996. Abstract No. H8.
75. Hayden FG. Combination antiviral therapy for respiratory virus infections. *Antiviral Research.* 1996;96:45–48.
76. Hayden FG, Treanor JJ, Betts RF, et al. Safety and efficacy of the neuraminadase inhibitor GG167 in experimental human influenza. *JAMA.* 1996;275:295–299.
77. Hromas R, Cornetta K, Srour E, et al. Donor leukocyte infusion as therapy for life-threatening adenoviral infections after T-cell depleted bone marrow transplantation. (Letter) *Blood.* 1994;84:1689–1690.

DISCUSSION

- PANEL LEADER: Donald Armstrong, MD, Chief of Infectious Diseases, Memorial Sloan Kettering, New York, New York

Does isolation of a virus from the lung mean that virus is responsible for respiratory disease? Is there a way of quantifying the amount of virus versus the amount of disease it causes?

Dr. Robert B. Couch (Houston, Texas): Except for adenoviruses, which can be latent, isolation of one of the respiratory viruses from respiratory secretions indicates infection of the respiratory system with that virus. Since these viruses can produce disease, the disease that is occurring could be caused by the virus. But attributing the disease to the virus infection requires clinical correlation and consideration of other microbes detected. For the most part, no studies have been conducted to elucidate the cause-and-effect relationship between the isolation of a respiratory virus and the presence of a clinical disease pattern in immunocompromised persons, but they have been done for immunocompetent hosts.

For respiratory virus infections in immunocompromised hosts, greater amounts of virus generally correlate with a greater likelihood of disease and more severe disease. Although a great deal of disease is attributable to the immune response, and immune responses are impaired in immunocompromised patients, high levels of virus still should relate to occurrence of disease and its pattern. Quantitation of virus can be done using virus cultures, immune methods for antigen detection, quantitation of a property such as hemagglutinating activity, or quantitation by virus by gene detection using in situ hybridization or polymerase chain reaction.

Dr. Estella Whimbey (Houston, Texas): We frequently care for immunocompromised patients who have a clinical course consistent with a progressive viral pneumonia and who have influenza viruses, parainfluenza viruses, or picornaviruses isolated from their bronchoalveolar lavage fluid or endotracheal aspirates. Many of these patients die, and the histopathology at autopsy is reported as consistent with, but not diagnostic of, viral pneumonia, and no other pulmonary pathogens are identified. More sophisticated diagnostic tools need to be developed to confirm the specific etiology of these pneumonias.

Dr. Janet A. Englund (Houston, Texas): Whether they cause disease or not, it is abnormal to find these viruses repeatedly in respiratory secretions. To take the next step and state that the virus caused the disease, one needs the case histories and autopsy results. In the immunocompromised host, the isolation of one of these viruses on even one occasion should raise suspicion and concern. Even if the patient is asymptomatic at the time, the isolation of one of these viruses indicates a very high risk situation. In our experience, it frequently leads to more severe disease. Rather than debating whether it is or is not indicative of disease, perhaps it would be better to think of the finding in terms of whether it is normal or abnormal. With regard to quantitation, our work in autopsy-proven respiratory syncytial virus (RSV) pneumonia has shown that viral load is remarkably lower in adults than in children. It may be that adults have some partial immunity. Therefore, quantitation is going to be very difficult in the adult population.

Dr. Jack Remington (Palo Alto, California): According to the diagnostic laboratory that serves our institution, physicians rarely order viral cultures in immunocompromised patients. I believe one of the problems relates to the question of how to proceed if we do isolate a virus. We all need to address this question in our own institutions.

Dr. Donald Armstrong (New York, New York): We are now routinely looking for RSV and treating it with ribavirin. Even though I am not certain that the isolation of RSV signifies disease, I am quite certain that the isolation of RSV means that we should consider treating the patient.

Do respiratory viral infections occur more frequently in leukemia patients who have severe neutropenia immediately after chemotherapy? Does the neutrophil play a role? Should chemotherapy be delayed in patients with the "sniffles"?

Dr. Whimbey: The highest frequency of progression of RSV infections to serious pneumonias has been reported among patients with leukemia who have chemotherapy-induced myelosupression and among bone marrow transplant recipients whose marrow has not yet engrafted. When the neutrophil count rises to 500–1000 cells/mL, these patients seem to be better able to control these infections through their own immune defense mechanisms. Whether the neutrophil is important or whether it is a surrogate marker for some other host defense mechanism is not clear. It is of interest, however, that a high frequency of RSV pneumonia has not been reported among adult patients with profound cell-mediated immunodeficiency, such as patients infected with the human immunodeficiency virus (HIV).

With regard to the question of whether to delay chemotherapy in patients with upper respiratory tract illnesses, the decision must be made in the context of the particular virus causing the respiratory illness and the urgency of administering chemotherapy. For example, chemotherapy can more safely be postponed in a patient with chronic myelogenous leukemia in remission who is scheduled to receive a

0002-9343/97/$17.00 25
PII S0002-9343(97)00003-5

bone marrow transplant than in a patient with acute myelogenous leukemia in blast crises.

Dr. Gerald Bodey (Houston, Texas): We use the neutrophil count to measure the immune function of immunocompromised patients. However, we must recognize that these same patients have deficiencies in other host defense mechanisms that are not as easily measured. For example, a study we conducted several years ago showed that most patients with leukemia who had decreased neutrophil counts also had decreased lymphocyte counts. However, circulating levels of lymphocytes are not as accurate a reflection of the total lymphocyte population as levels of circulating neutrophils are in terms of the total neutrophil population. Chemotherapeutic agents also have an impact on macrophage function, antibody production, and a host of other factors, but these factors are more difficult to correlate with infection than are neutrophils.

Why are immunocompromised patients with viral respiratory infections more likely to develop pneumonia?

Dr. Couch: The numerous immune defects described for immunocompromised patients are sufficient to account for an increased level of viral infection and pure viral pneumonia. Although multiple factors are involved, the lower tract requires IgG antibody for prevention of infection and both IgG and cell-mediated immunity (primarily T cell cytotoxicity) for recovery. Both are defective in immunocompromised hosts. In addition, virus infection is known to impair host defenses against bacterial infection; so, the increased susceptibility these patients have to bacterial and fungal infections may be further increased by viral infection.

Dr. Armstrong: If we consider the mucosal damage to the gastrointestinal tract that occurs with many of the chemotherapeutic agents, we might postulate that the same thing is happening in the tracheal mucosa. However, effects on the tracheal mucosa have not been as well examined.

Dr. Whimbey: In terms of the role that damage to the respiratory tract mucosa might play in the etiology of serious respiratory disease, it is interesting to note that these viruses appear to cause more severe disease in lung transplant recipients than in other solid organ transplant recipients. This observation may provide a clue as to why patients who have chemotherapy-induced myelosuppression (and its associated mucositis) appear to be at greatest risk for developing serious lower respiratory tract disease.

Dr. Couch: Clearly, viruses can be spread by two methods: inhalation of small airborne particles or nasopharyngeal inoculation via large particles or direct contact. Most data suggest that the airborne mechanism is not a major factor in modern hospitals. Therefore, it is likely that deposition in the nasopharynx initiates infection in most cases. Infection of the nasopharynx, then, means an increased risk that the infection will descend to the lower respiratory tract. Data suggest that by treating early, when the infection is confined to the upper respiratory tract, one can prevent the descent to the lower respiratory tract that leads to viral pneumonia.

Dr. Raleigh A. Bowden (Seattle, Washington): I think one of the reasons for our perception that respiratory viruses are becoming a leading cause of fatal pneumonia is related to the progress we have made in controlling cytomegalovirus (CMV) infection. The occurrence of CMV pneumonia is no longer considerable in the early post-transplant period, for example, whereas fungal pneumonia and the respiratory viruses are becoming much more well appreciated.

Are morbidity and mortality from RSV infections more likely to occur in patients who have received allogeneic as opposed to autologous transplants?

Dr. Whimbey: At our center, we have not observed a higher frequency of serious RSV disease in allogeneic as opposed to autologous transplant recipients. However, our data have been somewhat skewed by the fact that the allogeneic transplant recipients are in a protected environment until their marrow recovers, and this may be the period of highest risk.

Dr. Bowden: There are differences in experiences from center to center and probably from one area of the country to another. Our experience has been that RSV infection is much more prominent in patients receiving allogeneic transplants, because these are primarily the types of patients we see; three quarters of our transplants are allogeneic and only one quarter are autologous. When pneumonia occurs, however, progression from the upper tract to the lower tract occurs at exactly the same rate in both types of transplant recipients. I do not know of any data demonstrating that allogeneic transplant recipients are at higher risk, even though one could propose many reasons why they might be. The data have not yet been assembled in a manner that would allow us to appreciate the full picture.